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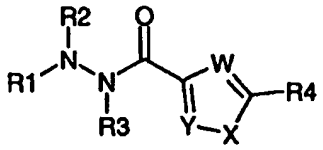


(I)

Compounds of formula (I), wherein $R^1$ is an aromatic or a heteroaromatic ring; $R^2$ and $R^3$ are H, $C_1$–$C_8$alkyl, aryl, aryl$C_1$–$C_8$alkyl, or heteroaryl; $R^4$ is an aromatic or a heteroaromatic ring or an amine; W, X, Y, are independently selected from the group consisting of CH, N, S, or O, provided that at least one of W, X, and Y is a heteroatom, which inhibit protease, including cathepsin K, pharmaceutical compositions of such compounds, and methods for treating diseases of excessive bone loss or cartilage or matrix degradation, including osteoporosis; gingival disease including gingivitis and periodontitis; arthritis, osteoarthritis and rheumatoid arthritis; Paget's disease; hypercalcemia of malignancy; and metabolic bone disease therewith.

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# PROTEASE INHIBITORS

## FIELD OF THE INVENTION

This invention relates in general to aryl and heteroaryl thiazoloketohydrazide protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

## BACKGROUND OF THE INVENTION

Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, and indicate an essential role for a cysteine proteases in bone resorption. For example, Delaisse, *et al.*, *Biochem. J.*, **1980**, *192*, 365, disclose a series of protease inhibitors in a mouse bone organ culture

system and suggest that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-$CHN_2$) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse, *et al.*, *Biochem. Biophys. Res. Commun.*, **1984**, *125*, 441, disclose that E-64 and leupeptin are also effective at preventing bone resorption *in vivo*, as measured by acute changes in serum calcium in rats on calcium deficient diets. Lerner, *et al.*, *J. Bone Min. Res.*, **1992**, *7*, 433, disclose that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies, such as by Delaisse, *et al.*, *Bone*, **1987**, *8*, 305, Hill, *et al.*, *J. Cell. Biochem.*, **1994**, *56*, 118, and Everts, *et al.*, *J. Cell. Physiol.*, **1992**, *150*, 221, also report a correlation between inhibition of cysteine protease activity and bone resorption. Tezuka, *et al.*, *J. Biol. Chem.*, **1994**, *269*, 1106, Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, **1995**, *206*, 89 and Shi, *et al.*, *FEBS Lett.*, **1995**, *357*, 129 disclose that under normal conditions cathepsin K (which has also been called cathepsin O), a cysteine protease, is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

Palmer, *et al.*, *J. Med. Chem.*, **1995**, *38*, 3193, disclose certain vinyl sulfones which irreversibly inhibit cysteine proteases, such as the cathepsins B, L, S, O2 and cruzain. Other classes of compounds, such as aldehydes, nitriles, α-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts and epoxy succinyl compounds have also been reported to inhibit cysteine proteases. The synthesis of azatides (polyacylhydrazides) as peptide mimetics has recently been disclosed by Han and Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539.

The synthesis of N-phenyl-N'-(2-phenyloxazol-4-ylcarbonyl)hydrazide, as well as its N-(2,4-dinitrophenyl) derivative, have been described in Afridi, A., et al., *J. Chem. Soc, Perkin Trans. I*, **1976**, *3*, 315-20. Benko, A.,et al., *Justus Liebigs Ann. Chem.*, **1968**, *717*, 148-53 describes the preparation of N-(4-ethoxycarbonylthiazol-2-yl)-N'-[2-(4-pyridinyl)thiazol-4-ylcarbonyl]hydrazide.

Thus, a structurally diverse variety of cysteine protease inhibitors have been identified. However, these known inhibitors are not considered suitable for use as therapeutic agents in animals, especially humans, because they suffer from various shortcomings. These shortcomings include lack of selectivity, cytotoxicity, poor solubility, and overly rapid plasma clearance. A need therefore exists for methods of treating diseases caused by pathological levels of proteases, especially cysteine proteases, including cathepsins, especially cathepsin K, and for novel inhibitor compounds useful in such methods.

We have now discovered a novel class of aryl and heteroaryl thiazoloketohydrazide compounds which are protease inhibitors, most particularly of cathepsin K.

## SUMMARY OF THE INVENTION

An object of the present invention is to provide aryl and heteroaryl thiazoloketohydrazide protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to Formula I.

In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

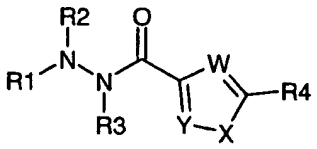
In yet another aspect, this invention provides intermediates useful in the preparation of the compounds of Formula I.

In still another aspect, this invention provides methods of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula I:




I

wherein:

$R^1$ is an aromatic ring, preferably phenyl or napthyl; or

a heteroaromatic ring comprising 1-4 heteroatoms independently selected from the group consisting of N,O, and S, preferably selected from the group consisting of the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7-napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl rings;

more preferably the quinolinyl or isoquinolinyl rings,

said aromatic ring or heteroaromatic ring being optionally independently mono- or di-substituted with $C_1$-8alkyl, $C_1$-8alkylether, $C_1$-8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, arylether, heteroarylether, aryl$C_1$-8alkylether, heteroaryl$C_1$-8alkylether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid;

$R^2$ and $R^3$ are independently H, $C_1$-8alkyl, aryl, aryl$C_1$-8alkyl, or heteroaryl;

$R^4$ is an aromatic ring, preferably phenyl or napthyl;

a heteroaromatic ring comprising 1-4 heteroatoms independently selected from the group consisting of N,O, and S, preferably selected from the group consisting of the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7-napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl rings;

said aromatic or heteroaromatic ring being optionally independently mono- or di- substituted with $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-8alkyl ether,

heteroaryl$C_1$-8alkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid; or

an amine, said amine being optionally independently mono- or di-substituted with $C_1$-$C_8$alkyl, aryl$C_0$-$C_8$alkyl, heteroaryl$C_0$-$C_8$alkyl; and

W,X,Y are independently selected from the group consisting of CH, N, S, or O, provided that at least one of W, X, and Y is a heteroatom; and

further provided that :

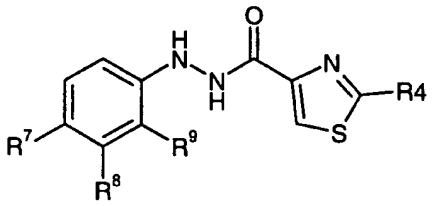
a) when W is N, X is O, and Y is CH, $R^4$ is not Ph; and

b) when $R^4$ is pyridinyl, $R^1$ is not $CO_2R'$-substituted thiazolyl;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

Compounds of Formula I wherein W = N, X = S, and Y = CH (thiazolo) are preferred. Even more preferred are such compounds wherein $R^1$ is aromatic, particularly phenyl or napthyl, or heteroaromatic, particularly quinolinyl, optionally independently mono- or di-substituted with $C_1$-8alkyl, $C_1$-$C_8$alkoxy ether, $C_1$-8alkylthioether, aryl$C_1$-8alkyl ether, heteroaryl$C_1$-8alkyl ether, arylaminocarbonyl or heteroarylaminocarbonyl and $R^2$ and $R^3$ are H.

Yet more preferred are compounds of Formula I, which may be conveniently represented by Formula II:




II

wherein:

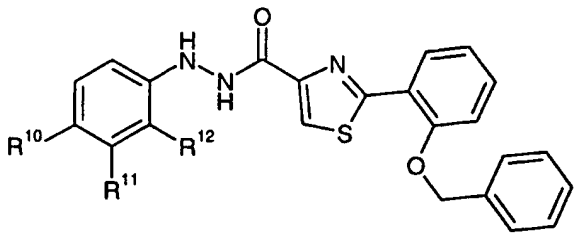
$R^7$ is selected from the group consisting of -H, -OPh, -$CH(CH_3)_2$, -OBn, and PhNHCO-;

$R^8$ is selected from the group consisting of H, $CH_3$, -$OCH_3$, and -OBn;

$R^9$ is selected from the group consisting of H, -$CH_2CH(CH_3)_2$, and Br, -$CH_2CH_3$, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, O $CH_3$, -CH(OH)Ph, and -$(CH_2)_2CH(CH_3)_2$;

$R^4$ is selected from the group consisting of 2-BnO($C_6H_4$)-, 1-napthyl, and -N[$(CH_2CH(CH_3)_2]$Ph.

Compounds of Formula I, which may be conveniently represented by Formula III are also more preferred:



III

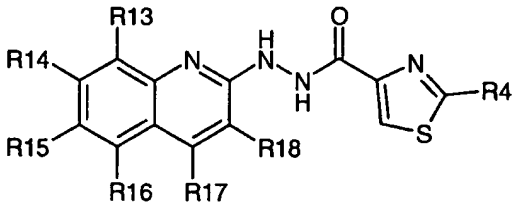
wherein:

$R^{10}$ is selected from the group consisting of -OBn, PhNHCO-, and (4-py)CH2O-;

$R^{11}$ is selected from the group consisting of $-OCH_2CH_2CH_3$, and $-OCH_2CH_3$;

$R^{12}$ is selected from the group consisting of -H, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $OCH_2CH_3$, $-OCH_2CH_2CH_3$ and $-OCH_2CH(CH_3)_2$.

Compounds of Formula I, which may be conveniently represented by Formula IV are also more preferred:



IV

wherein:

$R^4$ is as defined herein above for compounds of Formula I;

$R^{13}$ to $R^{18}$ are independently selected from the group consisting of $C_1$-8alkyl, $C_1$-8alkylether, $C_1$-8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, arylether, heteroarylether, aryl$C_1$-8alkylether, heteroaryl$C_1$-8alkylether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, and $C_1$-8 carboxylic acid.

The following compounds are particularly preferred embodiments of the present invention:

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(2-methylpropyl)-4-phenoxyphenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;

N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-(4-phenoxyphenyl)hydrazide;

N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-[4-(2-methylethyl)phenyl]hydrazide;

N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-phenylhydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)-2-bromophenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methylphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-phenylhydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-ethylphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propylphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(2-methylethyl)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-butylphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methylphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methoxyphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methoxyphenyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(α-hydroxybenzyl)phenyl[hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(N-phenylcarboxamido)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[3-(benzyloxy)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)-2-(3-methylbutyl)phenyl]hydrazide;

N-[2-(1-napthyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-pyridinyl)hydrazide; and

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-quinolinyl)hydrazide.

The following compounds are also particularly preferred embodiments of the present invention:

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-(benzyloxy)-2-(ethoxymethyl)phenyl}hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-(benzyloxy)-2-(methoxymethyl)phenyl}hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propoxy)-4-(N-phenylcarboxamido)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-ethoxy-4-(N-phenylcarboxamido)phenyl]hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-[(4-pyridinyl)carboxamido]phenyl}hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(4-pyridinylmethoxy)phenyl]hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-(3-methylbutyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(5-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methoxymethyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-methyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-butyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-propyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-phenyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(7-phenyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(6-phenyl-2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-methyl-N'-(2-quinolinyl)hydrazide;
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-propylhydrazide; and
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-ethylhydrazide.

The following compounds are most preferred embodiments of the present invention:

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazide; and
N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-quinolinyl)hydrazide.

**Definitions**

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of the present invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist

in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"$C_{1-8}$alkyl" as applied herein is meant to include, but is not limited to, substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl, hexyl, isohexyl, heptyl and octyl, and the simple aliphatic isomers thereof. Any $C_{1-8}$alkyl group may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. $C_0$alkyl means that no alkyl group is present in the moiety. Thus, Ar-$C_0$alkyl is equivalent to Ar.

"$C_{1-8}$ carboxylic acid" as applied herein is meant to include, but is not limited to, substituted and unsubstituted methanoic, ethanoic, n-propanoic, isopropanoic, n-butanoic, isobutanoic, sec-butanoic and t-butanoic, pentanoic, n-pentanoic, isopentanoic, neopentanoic, hexanoic, isohexanoic, heptanoic and octanoic acids, and the simple aliphatic isomers thereof. Any $C_{1-8}$ carboxylic acid group may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. $C_0$alkyl means that no alkyl group is present in the moiety. Thus, Ar-$C_0$alkyl is equivalent to Ar.

"$C_{1-8}$alkylamine" as applied herein is meant to include, but is not limited to, substituted and unsubstituted methylamine, ethylamine, n-propylamine, isopropylamine, n-butylamine, isobutylamine, sec-butylamine, t-butylamine, n-pentylamine, isopentylamine, neopentylamine, hexylamine, iohexylamine, heptylamine and octylamine and the simple aliphatic isomers thereof. Any $C_{1-8}$alkylamine may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. $C_0$alkylamine means that no alkyl group is present in the moiety. Thus, $C_0$alkylamine is equivalent to amine.

"Aryl ether" as applied herein is meant to include, but is not limited to, substituted and unsubstituted phenyl ether and napthyl ether. Any aryl ether may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Heteroaryl ether" as applied herein is meant to include, but is not limited to, substituted and unsubstituted pyridinyl ether, quinolino ether, isoquinolo ether, pyrimidinyl ether, pyrrolo ether, imidazolo ether, triazolo ether, tetrazolo ether, indolo ether, benzimidazolo ether, furo ether, benzofuro ether, thieno ether, benzothieno ether, oxazolo ether, thiazolo ether, benzoxazolo ether, benzothiazolo ether, isoxazolo ether, benzisoxazolo ether, isothiazolo ether and benzoisothiazolo ether. Any heteroaryl ether may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Aryl$C_{0-8}$alkyl ether" as applied herein is meant to include, but is not limited to, substituted and unsubstituted benzylether,phenethyl ether, phenyl-n-propyl ether, phenyl-n-propyl ether, phenylisopropyl ether, phenyl-n-butyl ether, phenylisobutyl ether, phenyl-sec-butyl ether, phenyl-t-butyl ether, phenyl-n-pentyl ether, phenylisopentyl ether, phenylneopentyl ether, phenylhexyl ether, phenylisohexyl ether, phenylheptyl ether, phenyloctyl ether, napthylmethyl ether and napthylethyl ether octylamine and the simple aliphatic isomers thereof. Any aryl$C_{1-8}$alkyl ether may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. Aryl$C_0$alkyl ether means that no alkyl group is present in the moiety. Thus, aryl$C_0$alkyl ether is equivalent to aryl ether.

"Heteroaryl$C_{0-8}$alkyl ether" as applied herein is meant to include, but is not limited to, substituted and unsubstituted pyridinylmethyl ether, pyridinylethyl ether, pyridinyl-n-propyl ether, pyridinylisopropyl ether, pyridinyl-n-butyl ether, pyridinylisobutyl ether, pyridinyl-sec-butyl ether, pyridinyl-t-butyl ether, pyridinyl-n-pentyl ether, pyridinylisopentyl ether, pyridinylneopentyl ether, pyridinylhexyl ether, pyridinylisohexyl ether, pyridinylheptyl ether, pyridinyloctyl ether, pyrimidinylmethyl ether and pyrimidinylethyl ether octylamine and the simple aliphatic isomers thereof. Any heteroaryl$C_{1-8}$alkyl ether may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. Heteroaryl$C_0$alkyl ether means that no alkyl group is present in the moiety. Thus, heteroaryl$C_0$alkyl ether is equivalent to heteroaryl ether.

"Arylaminocarbonyl" as applied herein is meant to include, but is not limited to, substituted and unsubstituted anilinocarbonyl and napthylaminocarbonyl. Any arylaminocarbonyl may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Heteroarylaminocarbonyl" as applied herein is meant to include, but is not limited to, substituted and unsubstituted pyridinylaminocarbonyl, quinoloaminocarbonyl, isoquinoloaminocarbonyl, pyrimidinylaminocarbonyl, pyrroloaminocarbonyl, imidazoloaminocarbonyl, triazoloaminocarbonyl, tetrazoloaminocarbonyl, indoloaminocarbonyl, benzimidazoloaminocarbonyl, furoaminocarbonyl, benzofuroaminocarbonyl, thienoaminocarbonyl, benzothienoaminocarbonyl, oxazoloaminocarbonyl, thiazoloaminocarbonyl, benzoxazoloaminocarbonyl, benzothiazoloaminocarbonyl, isoxazoloaminocarbonyl, benzisoxazoloaminocarbonyl, isothiazoloaminocarbonyl and benzoisothiazoloaminocarbonyl. Any heteroarylaminocarbonyl may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Aryl$C_0$-$C_6$alkylamine" as applied herein is meant to include, but is not limited to, substituted and unsubstituted aniline, benzylamine, phenethylamine, phenyl-n-propylamine, phenylisopropylamine, phenyl-n-butylamine, phenylisobutylamine, phenyl-sec-butylamine, phenyl-t-butylamine, phenyl-n-pentylamine, phenylisopentylamine, phenylneopentylamine, phenylhexylamine, phenylisohexylamine, napthylmethylamine amd napthylethylamine octylamine and the simple aliphatic isomers thereof. Any aryl$C_1$-$_8$alkylamine may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. Aryl$C_0$alkylamine means that no alkyl group is present in the moiety. Thus, aryl$C_0$alkylamine is equivalent to arylamine.

"Heteroaryl$C_0$-$C_6$alkylamine" as applied herein is meant to include, but is not limited to, substituted and unsubstituted pyridinylamine, pyridinylmethylamine, pyridinylethylamine, pyridinyl-n-propylamine, pyridinylisopropylamine, pyridinyl-n-butylamine, pyridinylisobutylamine, pyridinyl-sec-butylamine, pyridinyl-t-butylamine, pyridinyl-n-pentylamine, pyridinylisopentylamine, pyridinylneopentylamine, pyridinylhexylamine, pyridinylisohexylamine, pyrimidinylmethylamine and pyrimidinylethylamine octylamine and the simple aliphatic isomers thereof. Any $C_1$-$_8$alkylamine may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl. Heteroaryl$C_0$alkylamine means that no alkyl group is present in the moiety. Thus, heteroaryl$C_0$alkylamine is equivalent to heteroarylamine.

"Arylamine" as applied herein is meant to include, but is not limited to, substituted and unsubstituted aniline and napthylamine. Any arylamine may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Heteroarylamine" as applied herein is meant to include, but is not limited to, substituted and unsubstituted pyridinylamine, quinoloamine, isoquinoloamine,

pyrimidinylamine, pyrroloamine, imidazoloamine, triazoloamine, tetrazoloamine, indoloamine, benzimidazoloamine, furoamine, benzofuroamine, thienoamine, benzothienoamine, oxazoloamine, thiazoloamine, benzoxazoloamine, benzothiazoloamine, isoxazoloamine, benzisoxazoloamine, isothiazoloamine and benzoisothiazoloamine. Any heteroarylamine may be optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or $C_{1-4}$alkyl, where R' is $C_{1-6}$alkyl.

"Halogen" means F, Cl, Br, and I.

"Ar" or "aryl" means phenyl or naphthyl, optionally substituted by one or more of Ph-$C_{0-6}$alkyl, Het-$C_{0-6}$alkyl, $C_{1-6}$alkoxy, Ph-$C_{0-6}$alkoxy, Het-$C_{0-6}$alkoxy, OH, $(CH_2)_{1-6}NR''R'''$, $O(CH_2)_{1-6}NR''R'''$; where $R'' = R''' = H$, $C_{1-6}$alkyl, Ar-$C_{0-6}$alkyl; Het-$C_{0-6}$alkyl, from $C_{1-4}$alkyl, OR', $N(R')_2$, SR', $CF_3$, $NO_2$, CN, $CO_2R'$, CON(R'), F, Cl, Br and I.

"Aromatic ring " means, particularly in reference to $R^1$ and $R^4$, phenyl or naphthyl.

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from $C_{1-4}$alkyl, OR', $N(R')_2$, SR', $CF_3$, $NO_2$, CN, $CO_2R'$, CON(R'), F, Cl, Br and I, where R' is $C_{1-6}$alkyl. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6-napthyridinyl, 1,7-napthyridinyl, 1,8-napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

"HetAr" or "heteroaryl" means any heterocyclic moiety encompassed by the above definition of Het which is aromatic in character, e.g., pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl,

pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

"Heteroaromatic ring " means, particularly in reference to $R^1$ and $R^4$; any stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is aromatic in character, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, , and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Exemplary heteroaromatic rings include the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8-napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl rings.

The term "heteroatom" as applied herein refers to oxygen, nitrogen and sulfur.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, sec-butyl refers to the secondary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, Bn or Bz or Bzl refer to the benzyl radical.

The term "mono-substituted", when used in reference to substituents on rings, e.g., aromatic or heteroaromatic rings, includes all permutations of single substituents at any one available ring position.

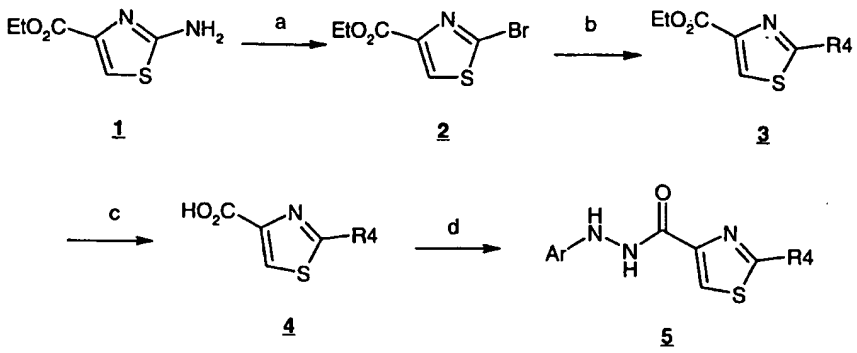
The term "di-substituted", when used in reference to substituents on rings, e.g., aromatic or heteroaromatic rings, includes all permutations and combinations of two substituents at any two available ring positions.

Certain reagents are abbreviated herein. EDC or EDCI refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBT or HOBt refers to 1-hydroxybenzotriazole, DMF refers to dimethyl formamide, $Pd(dppf)Cl_2$ refers to palladium bis(diphenylphosphino)ferrocene dichloride, DMPU refers to N,N-dimethylpropyleneurea, and THF refers to tetrahydrofuran.

**Methods of Preparation**

Compounds of Formula I where $R^1$ is unsubstituted, mono- or di-substituted phenyl, $R^2$ and $R^3$ is H and $R^4$ is 2-(benzyloxy)phenyl or 1-napthyl are prepared by methods analogous to those described in Scheme 1.

Scheme 1

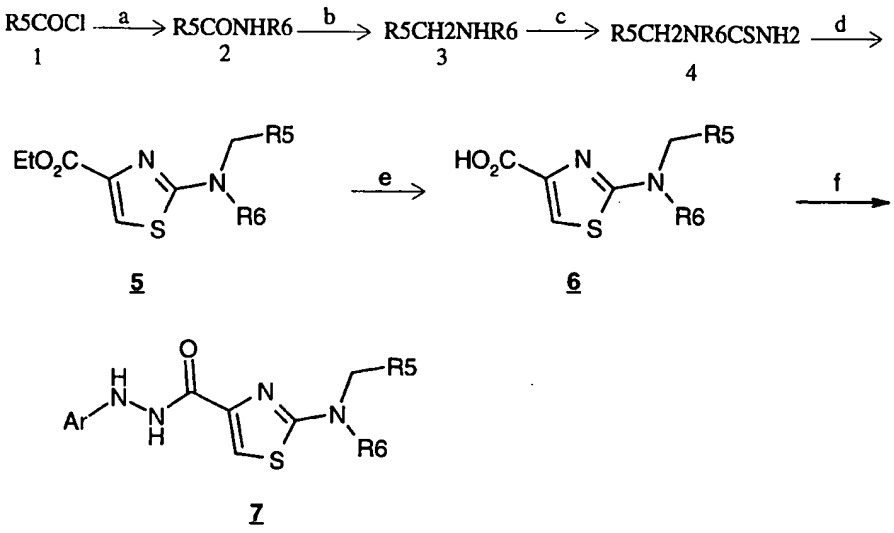



a)$NaNO_2$, HBr, CuBr, $H_2O$; b) $R^4B(OH)_2$, $Pd(PPh_3)_4$, EtOH, toluene; c)NaOH, MeOH; d)$ArNHNH_2$, EDCI.HCl, HOBt, DMF

The 2-aminothiazole 1-Scheme 1 is readily prepared by the condensation of thiourea with ethyl bromopyruvate in acetone at 45°C. Diazotisation of 1-Scheme 1 is performed with sodium nitrite in aqueous hydrobromic acid and the resulting diazo compound treated with copper bromide affording the bromothiazole 2-Scheme 1. Coupling of 2-Scheme 1 with an aryl boronic acid (such as 2-benzyloxyphenylboronic acid or 1-napthylboronic acid) is carried out using catalytic tetrakis(triphenylphospihe)palladium and a base (such as sodium hydrogen carbonate) in refluxing toluene/ethanol to afford 3-Scheme 1. Hydrolysis to the corresponding carboxylic acid 4-Scheme 1 occurs readily at room temperature on treatment with aqueous base (such as sodium hydroxide of lithium hydroxide) and the acid is condensed with an appropriate arylhydrazine (such as phenylhydrazine, 2-methylhydrazine, 4-phenoxyphenylhydrazine or 4-(benzyloxy)-2-(3-methylbutyl)phenylhydrazine) in the presence of a peptide coupling reagent (such as EDCI.HCl/HOBt) in an aprotic solvent (such as DMF) to provide 5-Scheme 1.

Compounds of the formula I where $R^1$ is unsubstituted, mono- or di-substituted phenyl or 1-napthyl, $R^2$ and $R^3$ is H and $R^4$ is $NR^5R^6$ where $R^5$ and $R^6$ is alkyl and/or aryl are prepared by methods analogous to those described in Scheme 2. An acid chloride (1-Scheme 2) is treated

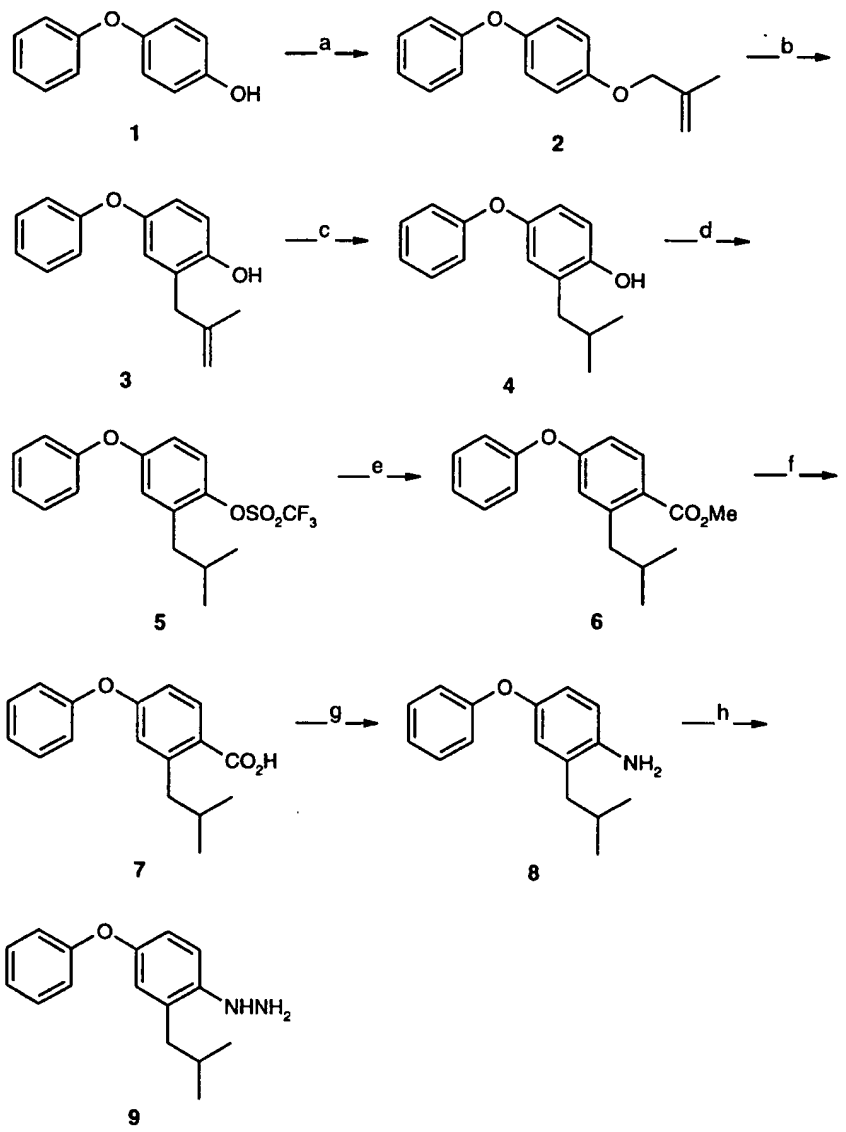
Scheme 2




a)$R^6NH_2$, Py, $CH_2Cl_2$; b) $LiAlH_4$, THF; c) i. $Cl_2CS$, Py, $CH_2Cl_2$; ii. $NH_3$, MeOH; d) $EtO_2CCOCH_2Br$, EtOH; e)NaOH, NaOH; f)$ArNHNH_2$ ,EDCI.HCl, HOBt, DMF

with a primary amine (such as 4-aminobiphenyl or aniline) and pyridine in an aprotic solvent (such as methylene chloride) to provide 2-Scheme 2, which is treated with lithium aluminum hydride in THF to afford 3-Scheme 2. Treatment of 3-Scheme 2 with thiophosgene and pyridine in methylene chloride, followed by treatment with ammonia in methanol provides 4-Scheme 2. Condensation with ethyl bromopyruvate gives 5-Scheme 2 which is then hydrolysed with aqueous base to afford the acid 6-Scheme 2. Condensation with an appropriate arylhydrazine (such as 4-phenoxyphenylhydrazine, 1-napthylhydrazine or 4-benzyloxyphenylhydrazine) in the presence of a peptide coupling reagent (such as EDCI.HCl/HOBt) in an aprotic solvent (such as DMF) provides arylhydrazides 7-Scheme 2.

Scheme 3

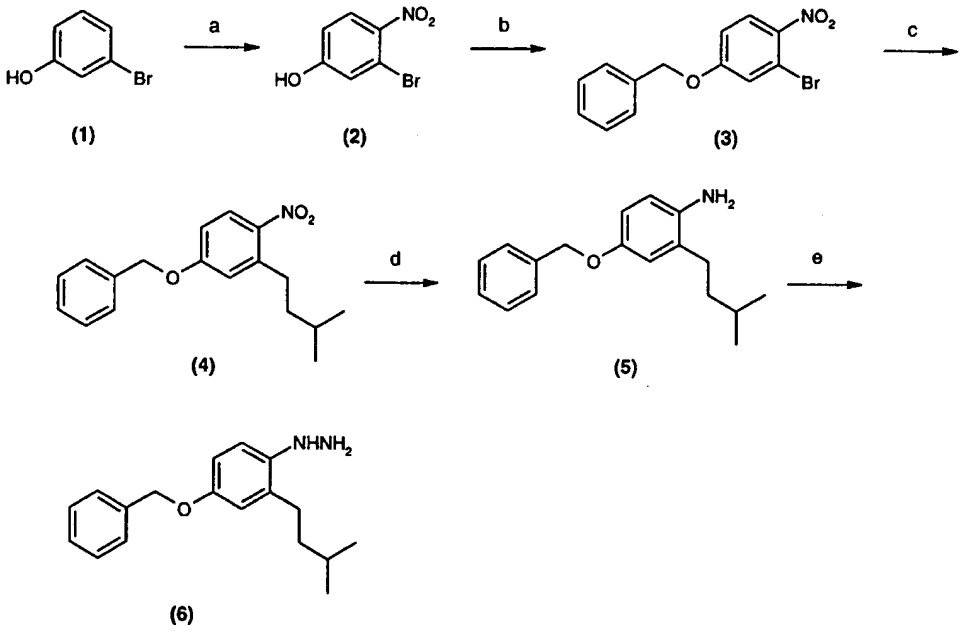



a) 3-bromo-2-methylpropene, $K_2CO_3$, acetone; b) heat; c) $H_2$, Pd-C, EtOH; d) NaH, $Ph(OTf)_2$, THF; e) $Pd(dppf)Cl_2$, $Et_3N$, MeOH, DMF; f) LiOH, THF; g) $Ph_2P(O)N_3$, $Et_3N$, toluene; NaOH; h) $NaNO_2$, HCl; $SnCl_2$, HCl.

Aryl hydrazines (such as 2-(2-methylpropyl)-4-phenoxyphenylhydrazine or 4-benzyloxy-2-(3-methylbutyl)phenylhydrazine) are prepared as described in Schemes 3 and 4. Treatment of 1-Scheme 3 with 3-bromo-2-methylpropene and potassium carbonate in acetone gives 2-Scheme 3, which is heated at 200 °C (neat) to provide 3-Scheme 3. Hydrogenation of 3-Scheme 3 in the presence of palladium on carbon in ethanol provides

4-Scheme 3, which is treated with sodium hydride and N-phenyltrifluorormethanesulfonimide in THF to afford 5-Scheme 3. Treatment of 5-Scheme 3 with a catalytic amount of tetrakis(triphenylphosphine)palladium, 1,1'-bis(diphenylphosphino)ferrocene, triethylamine and methanol in DMF gives 6-Scheme 3, which is hydrolyzed with lithium hydroxide in aqueous THF to provide 7-Scheme 3. Treatment of 7-Scheme 3 with diphenylphosphoryl azide and triethylamine in toluene followed by treatment with sodium hydroxide in aqueous THF provides 8-Scheme 3, which is subsequently treated with sodium nitrite in aqueous HCl, followed by treatment with $SnCl_2$ in aqueous HCl to provide the desired arylhydrazine 9-Scheme 3. 3-Bromophenol 1-Scheme 4 is treated with sodium nitrate in

Scheme 4

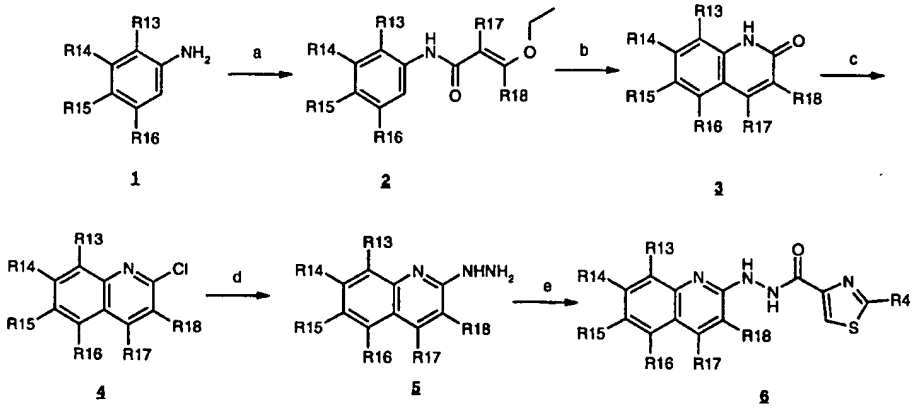



a) $NaNO_3$, HCl; b) BnBr, NaH, DMF; c) $Et_2Zn$, $MnBr_2$, CuCl, 3-methylbromobutane, $Pd(dppf)Cl_2$, THF, DMPU; d) $SnCl_2$, EtOH; e)$Me_3(C_6H_2)SO_3NH_2$, $Et_2O$, pet. ether.

concentrated HCl to afford 2-Scheme 4 which is alkylated with benzyl bromide in the presence of sodium hydride in DMF to give 3-Scheme 4. Treatement of 3-Scheme 4 with the organozinc reagent prepared from 3-methylbromobutane and diethyl zinc in DMPU and palladium bis(diphenylphosphino)ferrocene dichloride in THF at 65°C affords 4-Scheme 4. Reduction of the nitro group in 4-Scheme 4 occurs readily with tin dichloride to afford 5-Scheme 4 which is subsequently treated with O-trimethylbenzenesulfonylhydroxylamine to provide the desired arylhydrazine 6-Scheme 4. Other arylhydrazines were either

commercially available (such as 2-ethylphenylhydrazine or 4-(2-propyl)phenylhydrazine) or prepared from the corresponding commercially available amines (such as 2-butylaniline or 4-benzyloxyaniline) by processes similar to those described in Schemes 3 and 4.

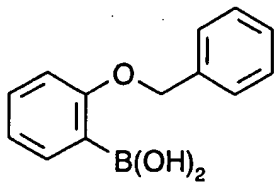
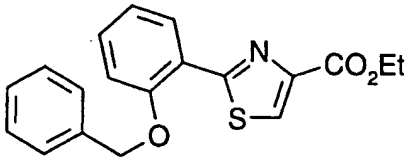
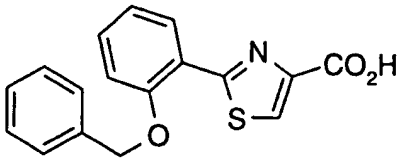
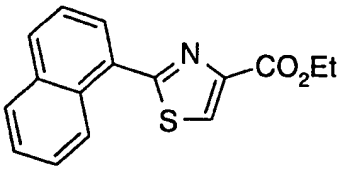
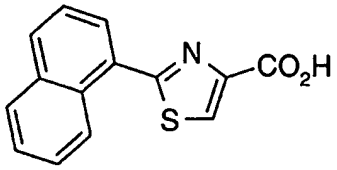
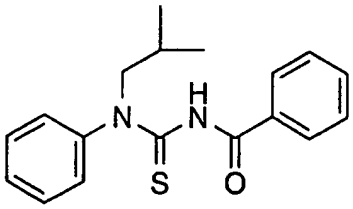
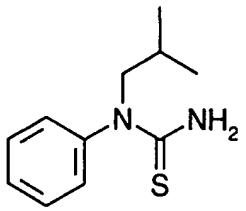
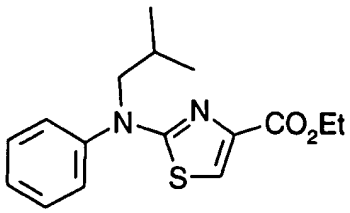
Compounds of the formula IV where $R^4$ is 2-(benzyloxy)phenyl or 1-napthyl and $R^{13}$ to $R^{18}$ are independently selected from the group consisting of $C_1$-$_8$alkyl, $C_1$-$_8$alkylether, $C_1$-$_8$alkylthioether, $C_1$-$_8$alkylamine, aryl, heteroaryl, arylether, heteroarylether, aryl$C_1$-$_8$alkylether, heteroaryl$C_1$-$_8$alkylether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, and $C_1$-$_8$ carboxylic acid are prepared by methods analogous to those described in Scheme 5. An appropriately substituted aniline such as 4-phenylaniline or 2-butylaniline 1-Scheme 5 is condensed with an alkoxyacryloyl chloride such as ethoxyacryloyl chloride to afford the amide 2-Scheme 5. Dehydrative cyclisation occurs on treatment of 2-Scheme 5 with an appropriate acid (such as concentrated sulfuric acid or polyphosphoric acid) to give the quinolone 3-Scheme 5. Treatment with phosphorous oxychloride then affords 4-Scheme 5 which is treated with excess hydrazine in refluxing ethanol to afford the hydrazinoquinoline 5-Scheme 5. Condensation with an appropriate carboxylic acid such as 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid or 2-(1-napthyl)thiazole-4-carboxylic acid in the presence of a peptide coupling reagent (such as EDCI.HCl/HOBt) in an aprotic solvent (such as DMF) provides quinolinylhydrazides 6-Scheme 5.

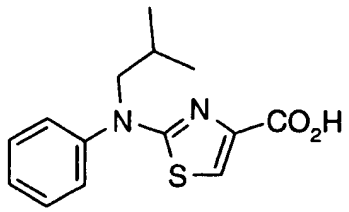



Scheme 5

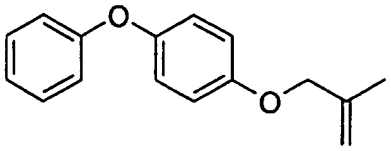
a) EtOC(R17)=C(R18)COCl, pyridine; b) $H_2SO4$; c) $POCl_3$; d) $NH_2NH_2$, EtOH; e) R4-thiazole)-$CO_2H$, EDCI, HOBt, DMF.

The following compounds of the present invention are useful as intermediates in the synthesis of the Compounds of Formulas I, II, III and IV.

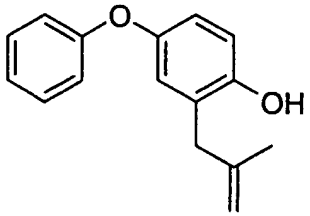
| Structure | Chemical Name |
|---|---|
|  | 2-benzyloxyphenylboronic acid |
|  | ethyl 2-(2-benzyloxyphenyl)thiazol-4-carboxylate |
|  | 2-(2-benzyloxyphenyl)thiazol-4-carboxylic acid |
|  | ethyl 2-(1-naphthyl)thiazol-4-carboxylate |
|  | 2-(1-naphthyl)thiazol-4-carboxylic acid |
|  | N-benzoyl-N'-(2-methyl-1-propyl)-N'-phenylthiourea |
|  | N-(2-methyl-1-propyl)-N-phenylthiourea |
|  | ethyl 2-[N-(2-methyl-1-propyl)-N-phenyl amino]thiazole-4-carboxylate |



2-[N-(2-methyl-1-propyl)-N-phenyl amino]thiazole-4-carboxylic acid



2-methyl-3-(4-phenoxyphenoxy)propene



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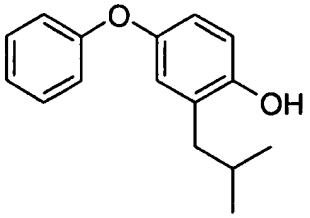

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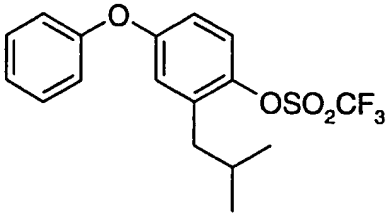

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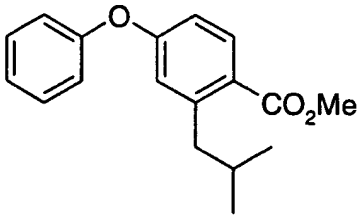
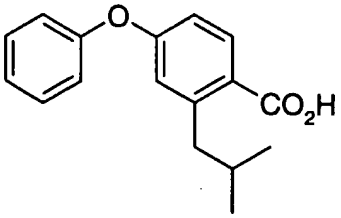


methyl 2-(2-methylpropyl)-4-phenoxybenzoate



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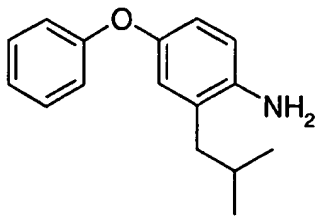
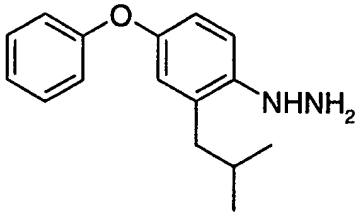
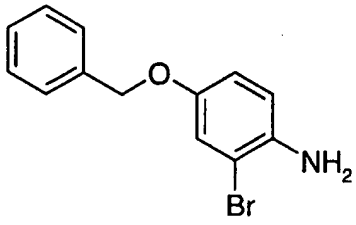


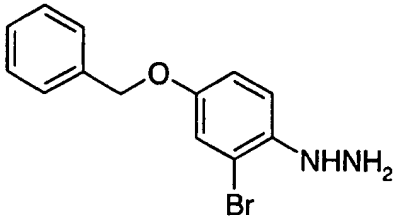

2-(2-methylpropyl)-4-phenoxyaniline



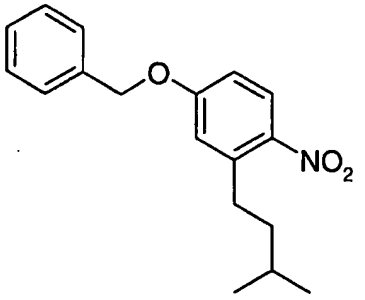

2-(2-methylpropyl)-4-phenoxyphenylhydrazine



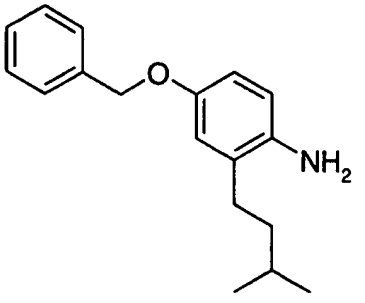

2-bromo-4-benzyloxyaniline



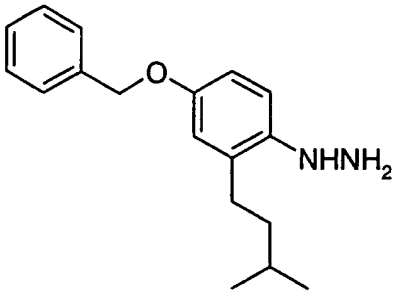

2-bromo-4-benzyloxyphenylhydrazine



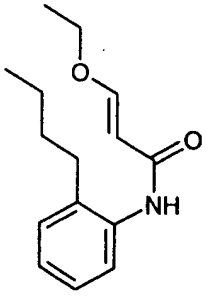

4-benzyloxy-2-(3-methylbutyl)nitrobenzene



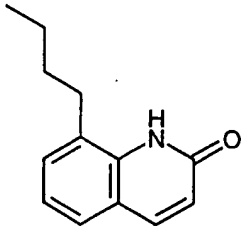

4-benzyloxy-2-(3-methylbutyl)aniline



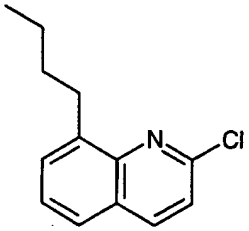
4-benzyloxy-2-(3-methylbutyl)phenylhydrazine



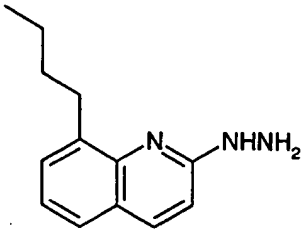
*trans*-3-ethoxy-(2-butylphenyl)acrylamide



8-butylquinolin-2-one



8-butyl-2-chloroquinoline



8-butyl-2-hydrazinoquinoline

The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of Formula I are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as $Li^+$, $Na^+$, $K^+$, $Ca^{++}$, $Mg^{++}$ and $NH_4^+$ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin,

hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

**Utility of the Present Invention**

The compounds of Formula I are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof an effective amount of a compound or combination of compounds of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof an effective amount of an inhibitor of cathepsin K, including a compound or combination of compounds of the present invention. The skilled artisan will understand that by the term "effective amount" is meant that amount of a compound or combination of compounds of the present invention sufficient to ameliorate or cure the clinically undesirable manifestations of disease (e.g. brittle and weakened bone in osteoporosis) caused by said pathological levels of target enzyme, e.g., cathepsin K, by inhibition of the target enzyme. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to an animal, particularly a mammal, most particularly a human in need thereof an effective amount of a compound or combination of compounds of Formula I, alone or in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of Formula I is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal

saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

**Biological Assays**

The compounds of the present invention may be tested in one of several biological assays to determine the concentration of compound which is required to provide a given pharmacological effect.

**Determination of cathepsin K proteolytic catalytic activity**

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

**Inhibition studies**

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al., Biochemitsry,* **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\,app}) + A] \qquad (1)$$

where $v$ is the velocity of the reaction with maximal velocity $V_m$ , $A$ is the concentration of substrate with Michaelis constant of $K_a$, and $I$ is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give $k_{obs}$ according to equation 2:

$$[AMC] = v_{ss}\, t + (v_0 - v_{ss})\,[1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time $t$, $v_0$ is the initial reaction velocity and $v_{ss}$ is the final steady state rate. Values for $k_{obs}$ were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant ($k_{obs}$ / inhibitor concentration or $k_{obs}$ / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al., Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

**Human Osteoclast Resorption Assay**

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes

away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to $1.5x10^4$/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension ( per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

**General**

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-$d_6$ is hexadeuteriodimethylsulfoxide, and $CD_3OD$ is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt =

doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers ($cm^{-1}$). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

**Examples**

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

Preparation of N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazine

a) ethyl 2-aminothiazole-4-carboxylate hydrobromide

To a stirring suspension of thiourea (6.0 g, 78.8 mmol) in ethanol (80 mL) was added ethyl bromopyruvate (15.4 g, 78.8 mmol). The resulting solution was heated at 45 °C for 23 h. The solution was cooled at 0 °C for 24 h, and the crystals were collected by filtration and washed with cold ethanol to provide the title compound (15.8 g, 79%). $^1H$ NMR (400 MHz, $CD_3OD$) d 7.70 (s, 1H), 4.41 (q, 2H), 1.38 (t, 3H).

b) ethyl 2-bromothiazole-4-carboxylate

To a stirring suspension of the compound of Example 1(a) (12.15 g, 48 mmol) in 16% aqueous HBr (150 mL), cooled to 0 °C, was added drropwise a solution of sodium nitrite (3.44 g, 49.8 mmol) in water (6 mL). After stirring for 35 min, copper (I) bromide (7.83 g, 54.6 mmol) and 16% aqueous HBr (60 mL) were added and the mixture was heated at 70 °C for 1 h. The mixture was filtered and the filtrate was saturated with NaCl then extracted with ethyl acetate (2 X 170 mL). The combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The residue was combined with the solid collected in the first filtration, heated at reflux in ethanol (500 mL) for 5 min, then filtered. To the filtrate was added 1.5 mL of 48% aqueous HBr and the solution was heated at reflux for 16 h, then concentrated. The residue was partitioned between saturated aqueous $NaHCO_3$ and ethyl acetate. The organic layer was washed with saturated brine, dried (MgSO4), decolorized with charcoal, filtered and concentrated to provide the title compound as a pale yellow solid (7.46 g, 75%). MS (ESI): 236.0 $(M+H)^+$.

c) 2-benzyloxybromobenzene

To a stirring solution of 2-bromophenol (10.0 g, 57.8 mmol), and benzyl bromide (9.9 g, 57.8 mmol) in acetone (150 mL) was added $K_2CO_3$ (12.0 g, 86.7 mmol). After stirring at reflux for 4h, the mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a colorless oil (15.2 g, 57.8 mmol). $^1$HNMR (400 MHz, $CDCl_3$) d 7.62 (m, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.37 (m, 1H), 7.28 (m, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 5.17 (s, 2H).

d) 2-benzyloxyphenylboronic acid

To a stirring solution of the compound of Example 1(c) (15.2 g, 57.8 mmol) in THF (100 mL) at -78°C was added dropwise *n*-BuLi (23.1 mL, 2.5M in hexane, 57.8 mmol). The mixture stirred at -78°C for 25 min when added via cannulation to a stirring solution of triisopropylborate (54.4 g, 289 mmol) in THF (100 mL) at -78°C. After warming to room temperature and stirring for 3h, the mixture was poured into 3N HCl (100 mL) and extracted with ethyl acetate (3 X 200mL). The organic layers were combined, washed successively with water and brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane) to yield the title compound as a pale yellow solid (6.9 g, 30.3 mmol). $^1$HNMR (400 MHz, $CDCl_3$) d 7.90 (d, 1H), 7.42 (m, 6H), 7.07 (t, 1H), 7.02 (d, 1H), 6.05 (s, 2H), 5.16 (s, 2H).

e) ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate

To a stirring solution of the compound of Example 1(b) (4.0 g, 16.9 mmol), the compound of Example 1(d) (4.29 g, 18.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.65 g, 0.57 mmol) in dimethoxyethane (60 mL) was added cesium fluoride (8.58 g, 56.5 mmol) and the mixture was heated at 85 °C for 16 h. Tetrakis(triphenylphosphine)palladium(0) (0.65 g, 057 mmol) was added and heating at 85 °C was continued for 5 h. The mixture was diluted with water (60 mL) and extracted with ethyl acetate (2 X 120 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on 180 g of 230-400 mesh silica gel, eluting with 15% ethyl acetate in hexanes, to provide the title compound as a white solid (3.22 g, 56%). MS (ESI): 340.3 $(M+H)^+$.

f) 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid

To a stirring solution of the compound of Example 1(e) (184.2 mg, 0.54 mmol) in 1:1 THF/water (4 mL) was added lithium hydroxide monohydrate (68.3 mg, 1.63 mmol). The mixture was allowed to stir for 5 h at room temperature, then acidified with 1 N HCl and extracted with ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to give the title compound as an off-white solid (165.5 mg, 98%). MS (ESI): 312.2 $(M-H)^-$.

g) 4-phenoxyphenylhydrazine

To a stirring suspension of 4-phenoxyaniline (1.0 g, 5.4 mmol) in concentrated HCl (4 mL), cooled to -10 °C, was added dropwise a solution of sodium nitrite (0.38 g, 5.47 mmol) in water (1 mL). The mixture was sallowed to stir at -10 °C for 20 min, then poured into a stirring -10 °C solution of $SnCl_2$ (2.45 g, 12.9 mmol) in concentrated HCl (15 mL). The resulting mixture was allowed to stir at -10 °C for 20 min, then brought to pH 14 with 10% aqueous NaOH. The mixture was extracted with methylene chloride and the extract was washed with water and saturated brine, then dried ($MgSO_4$), filtered and concentrated to leave the title compound as a pale yellow solid (1.063 g, 98%). $^1$HNMR (400 MHz, $CDCl_3$) d 7.37-7.28 (m, 2H), 7.06-6.84 (m, 7H), 5.15 (brs, 1H), 3.60 (brs, 2H).

h) N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazine

A solution of the compound of Example 1(f) (55.7 mg, 0.18 mmol), the compound of Example 1(g) (39.4 mg, 0.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (837.7 mg, 0.2 mmol), and 1-hydroxybenzotriazole (5.3 mg (0.04 mmol) in DMF (0.4 mL) was allowed to stir at room temperature for 21 h. The solution was diluted

with ethyl acetate and washed with saturated aqueous $NaHCO_3$, water (2X) and saturated brine, then dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on 3 g of 230-400 mesh silica gel, eluting with 1:2 ethyl acetate/hexanes, to give the tltle compound as a pale yellow foam (67.7 mg, 77%). MS (ESI): 494.2 $(M+H)^+$.

Example 2

Preparation of N-[2-(1-naphthyl)thiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazine

Following the procedure of Example 1(e)-1(h), except substituting 1-maphthylboronic acid for 2-benzyloxyphenylboronic acid in step (e), the title compound was prepared (0.090g, 53%). MS(ESI): 438.1 $(M+H)^+$.

Example 3

Preparation of N-[2-[N-(2-methylpropyl)-N-phenyl]aminothiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazine

a) N-phenyl-2-methylpropionamide

Aniline (5.11 g, 54.87 mmol, 5.0 mL) and triethyl amine (5.55 g, 54.87 mmol, 7.65 mL) were dissolved in methylene chloride (30 mL), cooled to 0°C, and isobutyryl chloride (5.85 g, 54.87 mmol, 5.75 mL) was added dropwise. After stirring at 0°C for 1 h the mixture was diluted with methylene chloride (60 mL) and washed with 1 N NaOH, then with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue was washed with ether and dried to give the title compound as a pale yellow solid (6.695 g, 75%). MS (ESI): 164.1 $(M+H)^+$.

b) N-(2-methylpropyl)aniline

To a stirring solution of 1M $LiAlH_4$ (61.5 mmol, 61.5 mL) cooled to 0°C, was added slowly over 20 minutes a solution of the compound of Example 3(a) (6.695 g, 41.02 mmol) in 120 mL THF. After the addition was complete, the ice bath was removed and the solution was heated at 55 °C for 30 min. The mixture was cooled to 0°C and quenched with the addition of water (2.33 mL) 15% NaOH (2.33 mL) and water (7 mL). The solid was removed by filtration and washed with ether. The filtrate was evaporated to dryness to give the title compound as a brown liquid (5.52 g, 90%). MS (ESI): 150.0 $(M+H)^+$.

c) N-benzoyl-N'-(2-methylpropyl)-N'-phenylthiourea

The compound of Example 3(b) (1.883 g, 12.60 mmol) was dissolved in chloroform (20 mL) and benzoyl isothiocyanate (2.06 g, 12.60 mmol, 1.83 mL) was added. After stirring 45 min at room temperature, the solution was concentrated to provide the title compound as a yellow solid (3.94 g, 100%). MS (ESI): 335.3 $(M+Na)^+$.

d) N-(2-methylpropyl)-N-phenylthiourea

The compound of Example 3(c) (3.94 g, 12.60 mmol) was dissolved in methanol (120 mL) and water (100 mL), potassium carbonate (5.0 g, 36.2 mmol) was added and the solution was heated at reflux overnight. The reaction mixture was concentrated, redissolved in ethyl acetate, washed with sodium bicarbonate, water and dried ($MgSO_4$), filtered and concentrated to afford the title compound as a pale yellow solid (2.6 g, 100%). MS (ESI): 207.2 $(M-H)^-$.

e) ethyl 2-[N-(2-methylpropyl)-N-phenylamino]thiazole-4-carboxylate

The compound of Example 3(d) (2.90 g, 13.92 mmol) was dissolved in 35 mL of ethanol upon heating. The solution was cooled to room temperature and ethylbromopyruvate (2.71 g, 13.92 mmol, 1.75 mL) was added. The reaction mixture was heated at reflux for 10 min, then concentrated. The residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate and the combined organic phases were washed with saturated brine, dried over $MgSO_4$, filtered and concentrated to give an orange oil. The crude product was passed through silica gel, eluting with ethyl acetate/ hexane, (1:8, then 1:3) to give the title compound as a yellow solid (4.20 g, 100%). MS (ESI): 305.3 $(M+H)^+$.

f) N-[2-[N-(2-methylpropyl)-N-phenyl]aminothiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazine

Following the procedure of Example 1(f)-1(h), except substituting ethyl 2-[N-(2-methylpropyl)-N-phenylamino]thiazole-4-carboxylate for ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate in step (f), the title compound was prepared as an orange solid (60 mg, 33%). MS (ESI): 459.3 $(M+H)^+$.

Example 4

Preparation of N-[2-[N-(2-methylpropyl)-N-phenyl]aminothiazol-4-ylcarbonyl]-N'-[4-(2-propyl)phenyl]hydrazine

Following the procedure of Example 1(h), except substituting 2-[N-(2-methylpropyl)-N-phenylamino]thiazole-4-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid and 4-(2-propyl)phenylhydrazine (44 mg, 0.289 mmol) for 4-phenoxyphenylhydrazine, the title compound was obtained as a white solid (40 mg, 34%). MS (ESI): 409.3 $(M+H)^+$.

Example 5

Preparation of N-[2-[N-(2-methylpropyl)-N-phenyl]aminothiazol-4-ylcarbonyl]-N'-phenylhydrazine

Following the procedure of Example 1(h), except substituting 2-[N-(2-methylpropyl)-N-phenylamino]thiazole-4-carboxylic acid for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid, and phenylhydrazine (44 mg, 0.289 mmol) for 4-phenoxyphenylhydrazine, the title compound was obtained as a red solid (30 mg, 28%). MS (ESI): 367.2 $(M+H)^+$.

Example 6

Preparation of N-[2-[N-(2-methylpropyl)-N-phenyl]aminothiazol-4-ylcarbonyl]-N'-(1-naphthyl)hydrazine

Following the procedure of Example 1(e)-1(h), except substituting 1-naphthylboronic acid for 2-benzyloxyphenylboronic acid in step (e) and 1-naphthylhydrazine for 4-phenoxyphenylhydrazine in step (h), the title compound was prepared. MS(ESI): 396.2 $(M+H)^+$.

Example 7

Preparation of N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-[2-(2-methylpropyl)-4-phenoxyphenyl]hydrazine

a) 2-methyl-3-(4-phenoxyphenoxy)propene

A mixture of 4-phenoxyphenol (6.0 g, 32.2 mmol), 3-bromo-2-methylpropene (5.22 g, 38.7 mmol, 3.90 mL) and solid $K_2CO_3$ (6.68 g, 48.3 mmol) was heated at reflux for 21 h. The mixture was filtered and the filtrate was concentrated in vacuo to give the title compound as a colorless oil (7.74 g, 100%). $^1$HNMR (400 MHz, $CDCl_3$) d 7.31 (t, 2H), 7.05 (t, 1H), 6.99-6.90 (m, 6H), 5.11 (s, 1H), 5.01 (s, 1H), 4.43 (s, 2H), 1.85 (s, 3H).

b) 2-(2-methylpropenyl)-4-phenoxyphenol

The compound of Example 7(a) (3.53 g, 14.7 mmol) was heated in a sealed tube at 200 °C for 3 h to provide the title compound as a yellow oil (3.53 g, 100%). MS (ESI): 239.3 $(M-H)^-$.

c) 2-(2-methylpropyl)-4-phenoxyphenol

A mixture of the compound of Example 7(b) (3.53 g, 14.7 mmol) and 10% Pd-C (0.88 g) in ethanol (150 mL) was stirred under a balloon of hydrogen for 1 h. The mixture was filtered through a bed of celite and the filtrate was concentrated to give the title compound as a colorless oil ( 3.49 g, 98%). MS (ESI): 241.3 $(M-H)^-$.

d) 2-(2-methylpropyl)-4-phenoxyphenyltrifluoromethanesulfonate

To a suspension of sodium hydride (0.38 g, 15.8 mmol) in THF (30 mL), cooled to 0 °C, was added a solution of the compound of Example 7(c) ( 3.49 g, 14.4 mmol) in THF (4 mL). After 15 min, N-phenyltrifluoromethanesulfonimide (5.66 g, 15.8 mmol) was added and the mixture was allowed to stir at room temperature for 1 h. The mixture was diluted with 70 mL of ether and washed with 1 N NaOH (2X), water (2X) and satruated brine, then dried ($MgSO_4$), filtered and concentrated to give the title compound as a pale yellow oil (5.39 g, 100%). $^1$HNMR (250 MHz, $CDCl_3$) d 7.39 (t, 2H), 7.21-7.14 (m, 2H), 7.05-7.02 (m, 2H), 6.91-6.83 (m, 2H), 2.54 (d, 2H), 1.97-1.84 (m, 1H), 0.93 (d, 6H).

e) methyl 2-(2-methylpropyl)-4-phenoxybenzoate

A stirring solution of the compound of Example 7(d) (5.39 g, 14.4 mmol), palladium (II) acetate (97 mg, 0.43 mmol), 1,1'-bis(diphenylphsophine)ferrocene (479 mg, 0.86 mmol), triethylamine (2.91 g, 28.8 mmol, 4.0 mL) and methanol (9.23 g, 288 mmol,

11.7 mL) in DMF (30 mL) was heated under a balloon of CO at 60 °C for 1 h. The solution was diluted with ether (300 mL), washed with water (3X) and saturated brine, then dired ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on 120 g of 230-400 mesh silica gel, eluting with 2% ethyl acetate in hexanes to give the title compound as a colorless oil (2.58 g, 63%). $^1$HNMR (250 MHz, $CDCl_3$) d 7.92-7.89 (m, 1H), 7.42-7.35 (m, 2H), 7.21-7.14 (m, 1H), 7.08-7.04 (m, 2H), 6.84-6.80 (m, 2H), 3.88 (s, 3H), 2.84 (d, 2H), 1.94-1.78 (m, 1H), 0.90 (d, 6H).

f) 2-(2-methylpropyl)-4-phenoxybenzoic acid

Following the procedure of Example 1(f), except substituting methyl 2-(2-methylpropyl)-4-phenoxybenzoate for ethyl 2-(2-benzyloxyphenyl)thiazole-4-carboxylate, the title compound was prepared as a white crystalline solid (1.57 g, 64%). MS (ESI): 269.2 $(M-H)^-$.

g) 2-(2-methylpropyl)-4-phenoxyaniline

A stirring solution of the compound of Example 7(f) (200 mg, 0.74 mmol), diphenylphosphoryl azide (244.4 mg, 0.88 mmol, 0.2 mL) and triethylamine (79.6 mg, 0.79 mmol, 0.11 mL) in toluene (2.5 mL) was heated at 80 °C for 1 h. The solution was concentrated and the residue was dissolved in THF (2.5 mL) and 1 N NaOH (2.5 mL) was added. After stirring at room temperature for 15 min, the solution was siluted with water (10 mL) and extracted with ethyl acetate (15 mL). The extract was washed with water and saturated brine, then dried (MgSO4), filtered and concentrated to give the title compound as a pale yellow solid (144.6 mg, 81%). MS(ESI): 242.2 $(M+H)^+$.

h) N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-[2-(2-methylpropyl)-4-phenoxyphenyl]hydrazine

Following the procedure of Example 1(g)-1(h), except substituting 2-(2-methylpropyl)-4-phenoxyaniline for 4-phenoxyaniline in step (g), the title compound was prepared as a white crystalline solid (25.7 mg, 58%). MS (ESI): 550.3 $(M-H)^-$.

Example 8

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propylphenyl)hydrazine

a) 2-propylphenylhydrazine

Following the procedure of Example 1(g), except substituting 2-propylaniline for 4-phenoxyaniline, the title compound was prepared as an orange oil (1.0g, 62%). $^1$HNMR (300MHz, DMSO-d6) d 7.04 (m, 2H), 6.88 (d, 1H), 6.58-6.53 (m, 1H), 6.18 (brs, 1H), 3.97 (brs, 2H), 2.40 (t, 2H), 1.51 (m, 2H), 0.90 (t, 3H).

b) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propylphenyl)hydrazine

Following the procedure of Example 1(h), except substituting 4-propylphenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (155mg, 52%). MS (ESI): 444.1 $(M+H)^+$.

Example 9

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-butylphenyl)hydrazine

a) 2-butylphenylhydrazine

Following the procedure of Example 1(g), except substituting 2-butylaniline for 4-phenoxyaniline, the title compound was prepared as an orange oil (1.1g, 67%). $^1$HNMR (300MHz, DMSO-d6) d 7.04 (m, 2H), 6.89 (d, 1H), 6.59-6.50 (m, 1H), 6.17 (brs, 1H), 3.88 (brs, 2H), 2.42 (t, 2H), 1.46 (m, 2H), 1.32 (m, 2H), 0.89 (t, 3H).

b) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-butylphenyl)hydrazine

Following the procedure of Example 1(h), except substituting 4-butylphenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as an orange resin (189mg, 51%). MS (ESI): 458.2 $(M+H)^+$.

Example 10

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[3-(benzyloxy)phenyl]hydrazine

a) 3-(benzyloxy)phenylhydrazine

Following the procedure of Example 1(g), except substituting 3-benzyloxylaniline for 4-phenoxyaniline, the title compound was prepared as an orange solid (0.85g, 43%). $^1$HNMR (300MHz, DMSO-d6) d 7.50-7.29 (m, 5H), 6.97 (t, 1H), 6.69 (brs, 1H), 6.47 (s, 1H), 6.33 (dd, 1H), 6.23 (dd, 1H), 5.02 (s, 2H), 3.93 (brs, 2H).

b) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[3-(benzyloxy)phenyl]hydrazine

Following the procedure of Example 1(h), except substituting 3-(Benzyloxy)phenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (241mg, 37%). MS (ESI): 508.1 $(M+H)^+$.

Example 11

Preparation of N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-benzyloxyphenyl)hydrazine

a) 4-benzyloxyphenylhydrazine

Following the procedure of Example 1(g), except substituting 4-benzyloxyaniline for 4-phenoxyaniline, the title compound was prepared as a yellow solid (6.9g, 67%). $^1$HNMR (300MHz, $CDCl_3$) d 7.45-7.27 (m, 5H), 7.30 (d, 2H), 6.92 (d, 2H), 5.02 (s, 2H).

b) N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-benzyloxyphenyl)hydrazine

Following the procedure of Example 1(h), except substituting 4-benzyloxyphenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a yellow solid (82mg, 25%). MS (ESI): 508.2 $(M+H)^+$.

Example 12

Preparation of N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-benzyloxy-2-bromophenyl)hydrazine

a) 3-bromo-4-nitrophenol

3-Bromophenol (32.9g, 0.19mol) was added slowly to a cold (10°C) solution of sodium nitrate (29.0g, 0.34mol) in conc. sulfuric acid (40.0g) and water (70.0mL) and the resulting mixture was allowed to stir at room temperature for 2h. Water (200mL) was added and the resulting mixture was extracted with diethyl ether and the extract was dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (silica gel, 10% ethylacetate/hexanes) to afford first the undesired regioisomer 4-bromo-2-nitrophenol (8.1g, 20%), mp 40-42°C, then the title product as a yellow solid (12.7g, 31%). mp 125-127°C.

b) 4-benzyloxy-2-bromonitrobenzene

A solution of the compound from example 11(a) (12.7g, 58.3mmol) in DMF (150mL) was added dropwise to a cold (0°C) suspension of sodium hydride (60% in mineral oil)(2.4g, 61.2mmol) and the resulting mixture was stirred at 0°C for 15min. Benzyl bromide (6.93mL, 61.2mmol) was then added dropwise and the resulting mixture was stirred and heated at 50°C for 5h. The mixture was then allowed to cool to room temperature and quenched by addition of water (50.0mL). The mixture was extracted with ethyl acetate and the extracts were washed with water, saturated aqueous NaHCO3 and water, then dried ($MgSO_4$), filtered and concentrated. The residue was then crystallised from 20%ethyl acetate/hexanes to afford the title compound as off-white needles (12.6g, 70%). mp (ethyl acetate/hexanes) 73-74°C.

c) 4-benzyloxy-2-bromoaniline

A solution of the compound from example 11(b) (4.57g, 14.8mmol) in ethanol (50.0mL) was treated with tin dichloride dihydrate (16.7g,74.0mmol) and the solution was stirred and heated at 70°C for 1h. The mixture was allowed to cool to room temperature then poured onto ice-water. The resulting suspension was basified with 10% aqueous sodium hydroxide then extracted with ethyl acetate. The extracts were washed with saturated brine, then dried ($MgSO_4$) , filtered and concentrated to afford the title compound as a tan solid (3.79g, 92%). mp 50-53°C.

d) 4-benzyloxy-2-bromophenylhydrazine

To a solution of the compound from example 11(c) (625mg, 2.2mmol) in glacial acetic acid (10.0mL), water (4.0mL) and conc. hydrochloric acid (4.0mL) at 5°C was added a solution of sodium nitrite (171mg, 2.4mmol) in water (5.0mL) and the solution was stirred at 5°C for 15min. The resulting red solution was then added dropwise to a cold (5°C) solution of tin dichloride dihydrate (2.5g, 11.1mmol) in conc. hydrochloric acid (10.0mL) and the stirred mixture was allowed to warm to room temperature over 1h. The resulting suspension was basified with 10% aqueous sodium hydroxide then extracted with ethyl acetate. The extracts were washed with saturated brine, then dried ($MgSO_4$) , filtered and concentrated to afford the title compound as an orange solid (452mg, 70%). mp 78-79°C.

e) N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-(4-benzyloxy-2-bromophenyl)hydrazine

Following the procedure of Example 1(h), except substituting 4-benzyloxy-2-bromophenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a pale-orange solid (1.07g, 73%). MS (ESI): 588, 586 $[M+H]^+$.

Example 13

Preparation of N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-[4-benzyloxy-2-(3-methylbutyl)phenyl]hydrazine

a) 4-benzyloxy-2-(3-methylbutyl)nitrobenzene

To a suspension of manganese dibromide (140mg, 0.65mmol) in anhydrous DMPU (10.0mL) was added copper (I) chloride (42.9mg, 0.43mmol), 3-methyl-1-bromobutane (1.56mL, 13.0mmol) and diethyl zinc (0.5M solution in toluene)(11.2mL) then the resulting dark solution was stirred at room temperature for 4h then cooled to -30°C. A solution of the compound from example 11(b) (2.0g, 6.5mmol) in anhydrous THF (5.0mL) was then added followed by [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (212mg, 0.26mmol) then the mixture was stirred at room temperature for 1h followed by heating at 65°C for 16h. The solution was cooled to room temperature then quenched with 3N hydrochloric acid and extracted with diethyl ether. The extracts were washed with 3N hydrochloric acid, saturated aqueous $NaHCO_3$ and saturated brine then dried ($MgSO_4$) , filtered and concentrated to give an oil. This oil was purified by flash chromatography (silica gel, 2.5% diethyl ether/hexanes) to afford the title compound as a yellow oil (972mg, 50%). $^1$HNMR (300MHz, $CDCl_3$) d 8.01

(d, 1H), 7.43-7.27 (m, 5H), 6.89-6.83 (m, 2H), 5.13 (s, 2H), 2.95-2.89 (m, 2H), 1.68-1.47 (m, 3H), 0.95 (d, 6H).

b) 4-benzyloxy-2-(3-methylbutyl)aniline

Following the procedure of Example 11(c), except substituting 4-benzyloxy-2-(3-methylbutyl)nitrobenzene for 4-benzyloxy-2-bromonitrobenzene, the title compound was prepared as a tan solid (669mg, 77%). $^1$HNMR (300MHz, $CDCl_3$) d 7.45-7.29 (m, 5H), 6.71 (d, 1H), 6.69 (dd, 1H), 6.62 (d, 1H), 4.99 (s, 2H), 3.40 (brs, 2H), 2.50-2.44 (m, 2H), 1.71-1.38 (m, 3H), 0.96 (d, 6H).

c) 4-benzyloxy-2-(3-methylbutyl)phenylhydrazinium 2,4,6-trimethylbenzenesulfonate

A solution of the compound from example 13(b) (108mg, 0.40mmol) and O-(2,4,6-trimethylbenzenesulfonyl)hydroxylamine (0.40mmol) in diethyl ether (1.5mL) and petroleum ether (1.5mL) was stirred at room temperature for 10min. The precipitated solid was collected to afford the title compound as a colorless solid. $^1$HNMR (300MHz, $CDCl_3$) d 9.69 (brs, 3H), 7.44-7.28 (m, 5H), 6.98-6.86 (m, 3H), 6.76 (s, 2H), 5.08 (s, 2H), 2.51 (s, 6H) ,2.19 (s, 3H), 1.59-1.41 (m, 3H), 0.93 (d, 6H).

d) N-[2-(2-benzyloxy)phenylthiazol-4-ylcarbonyl]-N'-[4-benzyloxy-2-(3-methylbutyl)phenyl]hydrazine

Following the procedure of Example 1(h), except substituting 4-benzyloxy-2-(3-methylbutyl)phenylhydrazinium 2,4,6-trimethylbenzenesulfonate for 4-phenoxyphenylhydrazine and adding N-methylmorpholine (1.1eq.), the title compound was prepared as a colorless solid (120mg, 52%). . $^1$HNMR (300MHz, $CDCl_3$) d 9.30 (brs, 1H), 8.50 (d, 1H), 8.16 (s, 1H), 7.52-7.30 (m, 12H), 7.14 (t, 2H), 6.98 (d, 1H), 6.81 (d, 1H), 6.73 (dd, 1H), 5.33 (s, 2H), 5.00 (s, 2H), 2.69-2.64 (m, 2H), 1.70-1.55 (m, 3H), 0.98 (d, 6H).

## Example 14

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(a-hydroxybenzyl)phenyl] hydrazide

a) 2-(a-hydroxybenzyl)phenylhydrazide

A solution of 2-(a-hydroxybenzyl)aniline (7.1g, 36.0mmol) in 6N hydrochloric acid (100mL) was cooled to 0°C then treated dropwise with a solution of sodium nitrite (2.6g, 37.8mmol) in water (25.0mL). After 2min solid tin dichloride dihydrate (17.7g, 79.2mmol) was added and the solution was stirred and allowed to warm to room temperature over

30min. The resulting suspension was basified with 10% aqueous sodium hydroxide then extracted with dichloromethane. The extracts were washed with saturated brine, then dried ($MgSO_4$) , filtered and concentrated to afford the title compound as a yellow solid (3.8g, 49%), mp 112-113°C.

b) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(a-hydroxybenzyl)phenyl] hydrazide

Following the procedure of Example 1(h), except substituting 2-(a-hydroxybenzyl)phenylhydrazide for 4-phenoxyphenylhydrazine, the title compound was prepared as a tan solid (1.1g, 72%). mp 85-90°C. MS (ESI-) 506 $[M-H]^+$.

Example 15

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-pyridinyl)hydrazide

Following the procedure of Example 1(h), except substituting 2-hydrazinopyridine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.096g, 31%). MS (ESI): 403 $[M+H]^+$.

Example 16

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(2-methylethyl)phenyl]hydrazide

Following the procedure of Example 1(h), except substituting 4-(2-methylethyl)phenyhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.22g, 64%). MS (ESI): 444 $[M+H]^+$.

Example 17

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl) hydrazide

Following the procedure of Example 1(h), except substituting 1-naphthylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.28g, 80%). MS (ESI): 452 $[M+H]^+$.

Example 18

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-ethylphenyl)hydrazide

Following the procedure of Example 1(h), except substituting (2-ethylphenyl)hydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.28g, 86%). MS (ESI): 430 $[M+H]^+$.

Example 19

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methylphenyl)hydrazide

Following the procedure of Example 1(h), except substituting (2-methylphenyl)hydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.22g, 68%). MS (ESI): 416 $[M+H]^+$.

Example 20

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-phenylhydrazide

Following the procedure of Example 1(h), except substituting phenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.24g, 76%). MS (ESI): 402 $[M+H]^+$.

Example 21

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methoxyphenyl)hydrazide

Following the procedure of Example 1(h), except substituting 3-methoxyphenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.09g, 27%). MS (ESI): 432 $[M+H]^+$.

Example 22

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methylphenyl)hydrazide

Following the procedure of Example 1(h), except (3-methylphenyl)hydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.08g, 24%). MS (ESI): 416 $[M+H]^+$.

Example 23

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methoxyphenyl)hydrazide

Following the procedure of Example 1(h), except substituting 2-methoxyphenylhydrazine for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.14g, 41%). MS (ESI): 432.2 $[M+H]^+$.

Example 24

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(N-phenylcarboxamido)phenyl]hydrazide

a) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-benzoic acid)hydrazide

Following the procedure of Example 1(h), except substituting 4-hydrazinobenzoic acid for 4-phenoxyphenylhydrazine, the title compound was prepared as a white solid (0.28g, 78%). MS (ESI): 446 $[M+H]^+$.

b) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(N-phenylcarboxamido)phenyl]hydrazide

Following the procedure of Example 1(h), except substituting aniline for 4-phenoxyphenylhydrazine and the compound of Example 24(a) for 2-(2-benzyloxyphenyl)thiazole-4-carboxylic acid, the title compound was prepared as a white solid (0.020g, 6%). MS (ESI) 519 $[M-H]^-$.

Example 25

Preparation of N-(4-benzyloxyphenyl)-N-(3-methylbutyl)-N'-[2-(2-benzyloxy)phenyl(thazol-4-ylcarbonyl]hydrazine

a) N-(3-methylbutanoyl)-4-benzyloxyaniline

3-Methylbutanoyl chloride (6.14g, 50.9mmol) was added to a stirring mixture of benzyloxyaniline hydrochloride (10.0g, 42.4mmol), N,N-diisopropylethylamine (18.5ml, 106mmol) and 4-dimethylaminopyridine (0.26g, 2.0mmol) in dichloromethane (400ml) at 0°C. After 18 h, the reaction solution was washed with aqueous HCl (3N, 200ml), saturated sodium bicarbonate solution, brine then dried($MgSO_4$) and concentrated to yield the title compound as a white solid (10.9g, 99%). $^1$H NMR(300 MHz CDCl3) δ 7.44-7.32(m, 7H), 7.03(s, 1H), 6.93 (d, 2H), 5.05 (s, 2H), 2.20(d, 2H), 1.02(m, 7H).

b) N-(3-methylbutyl)-4-benzyloxyanilide

Borane methyl sulfide (24.0ml, 253mmol) was added to a stirring solution of the compound of Example 25(a) (10.9g, 38.5mmol) in THF (20 ml) at 0 °C. The resulting solution was heated under reflux for 6h. The mixture was concentrated to yield an oil. Aqueous HCl (6N, 10 ml) was added to yield a white solid which was filtered then triturated with diether ether to yield the title compound as a hydrochloride salt (10.1g, 86%). $^1$HNMR (300 MHz DMSO-$d_6$) δ 7.48-7.34(m, 7H), 7.15 (d, 2H), 5.14 (s, 2H),3.23(t, 2H), 1.67-1.60(m, 1H), 1.56-1.48 (m, 2H), 0.88(d, 6H). The HCl salt was teated with aqueous sodium hydroxide (10%). The aqueous solution was extracted with diethyl ether. The organic phase was washed with saturated sodium bicarbonate solution, brine, dried ($MgSO_4$), and concentrated in vacuo to yield the title compound (white solid).

c) N-(4-benzyloxyphenyl)-N-(3-methylbutyl)hydrazinium 2,4,6-trimethylbenzenesulfonate

Following the procedure of Example 13(c), except substituting N-(3-methylbutyl)-4-benzyloxyaniline for 4-benzyloxy-2-(3-methylbutyl)aniline, the title compound was prepared as a white solid (254 mg, 71%). MS (ESI): 285 $[M+H]^+$.

d) N-(4-benzyloxyphenyl)-N-(3-methylbutyl)-N'-[2-(2-benzyloxy)phenyl(thazol-4-ylcarbonyl]hydrazine

Following the procedure of Example 1(h), except substituting N-(4-benzyloxyphenyl)-N-(3-methylbutyl)hydrazinium 2,4,6-trimethylbenzenesulfonate for 4-phenoxyphenylhydrazine and adding N-methylmorpholine (1.1eq.), the title compound was prepared as a white solid (258mg, 86%). MS (ESI): 578 $[M+H]^+$.

Example 26

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-quinolinyl)hydrazide

Following the procedure of Example 1(h), except substituting 2-hydrazinoquinoline for 4-phenoxyphenylhydrazine, the title compound was prepared as a yellow solid. mp 228-230°C.

Example 27

Preparation of N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-butyl-2-quinolinyl)hydrazide

a) *trans*-3-ethoxy-(2-butylphenyl)acrylamide

A solution of 2-butylaniline (0.75g, 5mmole) in pyridine (10.0mL) was cooled to 0°C and treated in one portion with *trans*-3-ethoxyacryloyl chloride (0.74g, 5.5mmole). The solution was stitted at 0°C for 1h then diluted with water. The resulting precipitate was collected and washed with hexanes to yield the title compound as a cream solid (0.74g, 62%). mp 93-94°C; Anal. ($C_{15}H_{21}NO_2$) calcd: C, 72.8; H, 8.6; N, 5.7 found: C, 72.9; H, 8.6; N, 5.8.

b) 8-butylquinolin-2-one

Solid *trans*-3-ethoxy-(2-butylphenyl)acrylamide (0.70g, 2.8mmole) was added to stirred, concentrated sulphuric acid (10.0mL) at 0°C and the solution was allowed to slowly warm to room temp. with stirring over 2h. The brown solution was poured onto ice and filtered and the solid was washed with water to afford the title compound as a cream solid (0.47g, 83%). mp 127-128°C; Anal. ($C_{13}H_{15}NO$) calcd: C, 77.6; H, 7.5; N, 7.0 found: C, 77.2; H, 7.6; N, 7.0.

c) 8-butyl-2-chloroquinoline

A mixture of 8-butylquinolin-2-one (0.41g, 2.0mmole) and phosphorous oxychloride (10.0mL) was stirred and heated under reflux for 2h. The solution was evaporated and the residue diluted with chloroform. This solution was then washed with water, saturated sodium bicarbonate solution then brine, dried ($MgSO_4$) and evaporated to afford the title compound as a yellow oil (0.43g, 98%). Anal. ($C_{13}H_{14}NCl$) calcd: C, 71.0; H, 6.4; N, 6.4 found: C, 70.5; H, 6.3; N, 6.4.

d) 8-butyl-2-hydrazinoquinoline

A solution of 8-butyl-2-chloroquinoline (0.39g, 1.8mmole) in ethanol (10.0mL) was treated with anhydrous hydrazine (0.60mL, 18mmole) and the solution was heated under reflux for 16h. The solution was evaporated and the residue washed with hexanes to afford the title compound asd a cream solid (0.16g, 41%). MS (ESI): 216 $[M+H]^+$.

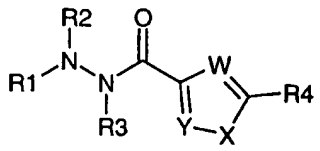
e) N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-butyl-2-quinolinyl)hydrazide

Following the procedure of Example 1(h), except substituting 8-butyl-2-hydrazinoquinoline for 4-phenoxyphenylhydrazine, the title compound was prepared as a cream solid (0.28g, 79%). mp (ethanol) 164-165°C. Anal. ($C_{30}H_{28}N_4O_2S$) calcd: C,70.8; H, 5.6; N, 11.0 found: C, 70.4; H, 5.7; N, 10.9.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

We claim:

1. A compound of Formula I:




I

wherein:

$R^1$ is an aromatic ring; or

a heteroaromatic ring comprising 1-4 heteroatoms independently selected from the group consisting of N,O, and S;

$R^2$ and $R^3$ are independently H, $C_1$-galkyl, aryl, aryl$C_1$-galkyl, or heteroaryl;

$R^4$ is an aromatic ring;

a heteroaromatic ring comprising 1-4 heteroatoms independently selected from the group consisting of N,O, and S; or

an amine;

and

W, X, and Y are independently selected from the group consisting of CH, N, S, and O;

provided that at least one of W, X, and Y is a heteroatom;

and further provided that:

a) when W is N, X is O, and Y is CH, $R^4$ is not Ph; and

b) when $R^4$ is pyridinyl, $R^1$ is not $CO_2R'$-substituted thiazolyl;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

2. A compound according to Claim 1 wherein $R^1$ is an aromatic ring.

3. A compound according to Claim 2 wherein said aromatic ring is phenyl or napthyl.

4. A compound according to Claim 2 wherein said aromatic ring is mono-substituted with a substituent selected from the group consisting of $C_1$-galkyl, $C_1$-galkylether, $C_1$-Cgalkylthioether, $C_1$-galkylamine, aryl, heteroaryl, arylether, heteroarylether, aryl$C_1$-

galkylether, heteroaryl$C_1$-galkylether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid;

5. A compound according to Claim 2 wherein said aromatic ring is di-substituted with substituents independently selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-galkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-galkyl ether, heteroaryl$C_1$-galkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid;

6. A compound according to Claim 1 wherein $R^1$ is a heteroaromatic ring.

7. A compound according to Claim 6 wherein said heteroaromatic ring is selected from the group consisting of the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl rings.

8. A compound according to Claim 7 wherein said heterocyclic ring is selected from the group consisting of the quinolyl and isoquinolyl rings.

9. A compound according to Claim 6 wherein said heteroaromatic ring is mono-substituted with a substituent selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-galkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-galkyl ether, heteroaryl$C_1$-galkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid.

10. A compound according to Claim 6 wherein said heteroaromatic ring is di-substituted with substituents independently selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-galkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-galkyl ether, heteroaryl$C_1$-galkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid.

11. A compound according to Claim 1 wherein $R^4$ is an aromatic ring.

12. A compound according to Claim 11 wherein said aromatic ring is phenyl or napthyl.

13. A compound according to Claim 11 wherein said aromatic ring is mono-substituted with a substituent selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-8alkyl ether, heteroaryl$C_1$-8alkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid.

14. A compound according to Claim 11 wherein said aromatic ring is di-substituted with substituents independently selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-8alkyl ether, heteroaryl$C_1$-8alkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid.

15. A compound according to Claim 1 wherein $R^4$ is a heteroaromatic ring.

16. A compound according to Claim 15 wherein said heteroaromatic ring is selected from the group consisting of the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl rings.

17. A compound according to Claim 15 wherein said heterocyclic ring is selected from the group consisting of the quinolyl and isoquinolyl rings.

18. A compound according to Claim 15 wherein said heteroaromatic ring is mono-substituted with a substituent selected from the group consisting of $C_1$-C8alkyl, $C_1$-C8alkyl ether, $C_1$-C8alkylthioether, $C_1$-8alkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-8alkyl ether, heteroaryl$C_1$-8alkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-8 carboxylic acid.

19. A compound according to Claim 15 wherein said heteroaromatic ring is di-substituted with substituents independently selected from the group consisting of $C_1$-

$C_8$alkyl, $C_1$-$C_8$alkyl ether, $C_1$-$C_8$alkylthioether, $C_1$-$_8$alkylamine, aryl, heteroaryl, aryl ether, heteroaryl ether, aryl$C_1$-$_8$alkyl ether, heteroaryl$C_1$-$_8$alkyl ether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, $C_1$-$_8$ carboxylic acid;

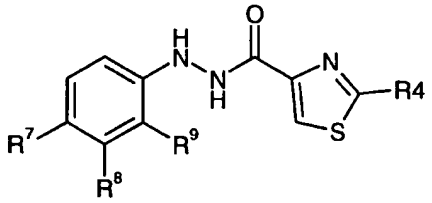
20. A compound according to Claim 1 wherein said amine is monosubstituted with a substituent selected from the group consisting $C_1$-$C_8$alkyl, aryl$C_0$-$C_8$alkyl, heteroaryl$C_0$-$C_8$alkyl.

21. A compound according to Claim 1 wherein said amine is disubstituted with substituents independently selected from the group consisting $C_1$-$C_8$alkyl, aryl$C_0$-$C_8$alkyl, heteroaryl$C_0$-$C_8$alkyl.

22. A compound according to Claim 1 wherein W = N, X = S, and Y = CH.

23. A compound according to Claim 22 wherein:
$R^1$ is an aromatic ring selected from the group consisting of phenyl and naphthyl;
$R^2$ and $R^3$ are H.

24. A compound according to Claim 1 of Formula II:




II

wherein:

$R^7$ is selected from the group consisting of -H, -OPh, -$CH(CH_3)_2$, -OBn, and PhNHCO-;

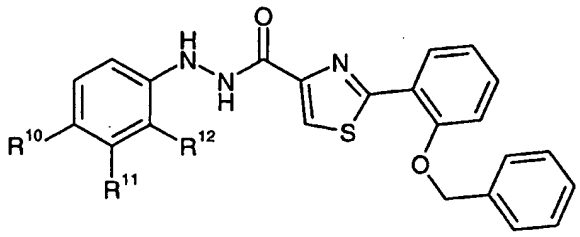
$R^8$ is selected from the group consisting of H, $CH_3$, -$OCH_3$, and -OBn;

$R^9$ is selected from the group consisting of H, -$CH_2CH(CH_3)_2$, and Br, -$CH_2CH_3$, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, O $CH_3$, -CH(OH)Ph, and -$(CH_2)_2CH(CH_3)_2$;

$R^4$ is selected from the group consisting of 2-BnO($C_6H_4$)-, 1-naphthyl, and -N[($CH_2CH(CH_3)_2$]Ph.

25. A compound according to Claim 24 wherein $R^4$ is quinoline.

26. A compound according to Claim 1 of Formula III:



III

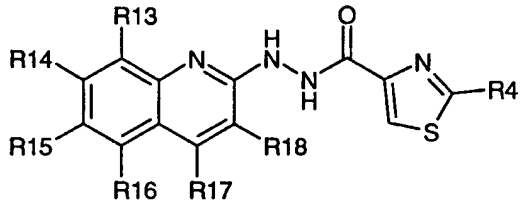
wherein:

$R^{10}$ is selected from the group consisting of -OBn, PhNHCO-, and (4-py)$CH_2O$-;

$R^{11}$ is selected from the group consisting of -$OCH_2CH_2CH_3$, and -$OCH_2CH_3$;

$R^{12}$ is selected from the group consisting of -H, -$CH_2OCH_2CH_3$, and -$CH_2OCH_3$, $OCH_2CH_3$, -$OCH_2CH_2CH_3$ and -$OCH_2CH(CH_3)_2$.

27. A compound according to Claim 1 of Formula IV:



IV

wherein:

$R^{13}$ to $R^{18}$ are independently selected from the group consisting of: $C_1$-$_8$alkyl, $C_1$-$_8$alkylether, $C_1$-$_8$alkylthioether, $C_1$-$_8$alkylamine, aryl, heteroaryl, arylether, heteroarylether, aryl$C_1$-$_8$alkylether, heteroaryl$C_1$-$_8$alkylether, arylaminocarbonyl, heteroarylaminocarbonyl, halogen, hydroxyl, thiol, and $C_1$-$_8$ carboxylic acid.

28. A compound according to Claim 1 selected from the group consisting of: N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-phenoxyphenyl)hydrazide; N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(2-methylpropyl)-4-phenoxyphenyl]hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;
N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-(4-phenoxyphenyl)hydrazide;
N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-[4-(2-methylethyl)phenyl]hydrazide;
N-{2-[N-(2-methylpropyl)-N-phenylamino]thiazol-4-ylcarbonyl}-N'-phenylhydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)-2-bromophenyl]hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methylphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-phenylhydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-ethylphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propylphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(2-methylethyl)phenyl]hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-butylphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methylphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-methoxyphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methoxyphenyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-(α-hydroxybenzyl)phenyl[hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(N-phenylcarboxamido)phenyl]hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[3-(benzyloxy)phenyl]hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)-2-(3-methylbutyl)phenyl]hydrazide;
N-[2-(1-napthyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(1-napthyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-pyridinyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-quinolinyl)hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-(benzyloxy)-2-(ethoxymethyl)phenyl}hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-(benzyloxy)-2-(methoxymethyl)phenyl}hydrazide;
N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(2-propoxy)-4-(N-phenylcarboxamido)phenyl]hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[2-ethoxy-4-(N-phenylcarboxamido)phenyl]hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-{4-[(4-pyridinyl)carboxamido]phenyl}hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(4-pyridinylmethoxy)phenyl]hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-(3-methylbutyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(5-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(3-methoxymethyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(4-methyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-butyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-propyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(8-phenyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(7-phenyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-(6-phenyl-2-quinolinyl)hydrazide;

N-[2-(2-benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-methyl-N'-(2-quinolinyl)hydrazide;

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-propylhydrazide; and

N-[2-(2-Benzyloxyphenyl)thiazol-4-ylcarbonyl]-N'-[4-(benzyloxy)phenyl]-N'-ethylhydrazide.

29. A compound according to Claim 28 which is N-[2-(2-benzyloxyphenyl)thiazol-4-carbonyl]-N'-(4-phenoxyphenyl)hydrazide.

30. A compound according to Claim 28 which is N-[2-(2-benzyoxyphenyl)thiazol-4-carbonyl]-N'-(2-quinolinyl)hydrazide.

31. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

32. A pharmaceutical composition comprising a compound according to Claim 28 and a pharmaceutically acceptable carrier, diluent or excipient.

33. A method of inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease, comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.

34. A method of inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease, comprising administering to a patient in need thereof an effective amount of a compound according to claim 28.

35. A method according to Claim 33 wherein said protease is a cysteine protease.

36. A method according to Claim 34 wherein said protease is a cysteine protease.

37. A method according to Claim 35 wherein said cysteine protease is cathepsin K.

38. A method according to Claim 36 wherein said cysteine protease is cathepsin K.

39. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Claim 1.

40. A method according to Claim 39 wherein said disease is osteoporosis.

41. A method according to Claim 39 wherein said disease is periodontitis.

42. A method according to Claim 39 wherein said disease is gingivitis.

43. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Claim 1.

44. A method according to Claim 43 wherein said disease is osteoarthritis.

45. A method according to Claim 43 wherein said disease is rheumatoid arthritis.

46. A method of treating a disease characterized by bone loss comprising inhibiting said bone loss by administering to a patient in need thereof an effective amount of a compound according to Claim 28.

47. A method according to Claim 46 wherein said disease is osteoporosis.

48. A method according to Claim 46 wherein said disease is periodontitis.

49. A method according to Claim 46 wherein said disease is gingivitis.

50. A method of treating a disease characterized by excessive cartilage or matrix degradation comprising inhibiting said excessive cartilage or matrix degradation by administering to a patient in need thereof an effective amount of a compound according to Claim 28.

51. A method according to Claim 50 wherein said disease is osteoarthritis.

52. A method according to Claim 50 wherein said disease is rheumatoid arthritis.

53. A compound selected from the group consisting of:
2-benzyloxyphenylboronic acid;
ethyl 2-(2-benzyloxyphenyl)thiazol-4-carboxylate;
2-(2-benzyloxyphenyl)thiazol-4-carboxylic acid;
ethyl 2-(1-naphthyl)thiazol-4-carboxylate;
2-(1-naphthyl)thiazol-4-carboxylic acid;
N-benzoyl-N'-(2-methyl-1-propyl)-N'-phenylthiourea;
N-(2-methyl-1-propyl)-N-phenylthiourea;
ethyl 2-[N-(2-methyl-1-propyl)-N-phenyl amino]thiazole-4-carboxylate;
2-[N-(2-methyl-1-propyl)-N-phenyl amino]thiazole-4-carboxylic acid;
2-methyl-3-(4-phenoxyphenoxy)propene;
2-(2-methylpropenyl)-4-phenoxyphenol;
2-(2-methylpropyl)-4-phenoxyphenol;
2-(2-methylpropyl)-4-phenoxyphenyltrifluoromethanesulfonate;
methyl 2-(2-methylpropyl)-4-phenoxybenzoate;
2-(2-methylpropyl)-4-phenoxybenzoic acid;
2-(2-methylpropyl)-4-phenoxyaniline;

2-(2-methylpropyl)-4-phenoxyphenylhydrazine;

2-bromo-4-benzyloxyaniline;

2-bromo-4-benzyloxyphenylhydrazine;

4-benzyloxy-2-(3-methylbutyl)nitrobenzene;

4-benzyloxy-2-(3-methylbutyl)aniline;

4-benzyloxy-2-(3-methylbutyl)phenylhydrazine;

*trans*-3-ethoxy-(2-butylphenyl)acrylamide;

8-butylquinolin-2-one;

8-butyl-2-chloroquinoline;

8-butyl-2-hydrazinoquinoline.

54. Use of a compound according to any one of Claims 1 to 30 in the manufacture of a medicament for use in inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease.

55. A use according to Claim 54 wherein said protease is a cysteine protease.

56. A use according to Claim 55 wherein said cysteine protease is cathepsin K.

57. Use of a compound according to any one of Claims 1 to 30 in the manufacture of a medicament for use in treating a disease characterized by bone loss.

58. A use according to Claim 57 wherein said disease is osteoporosis.

59. A use according to Claim 57 wherein said disease is periodontitis.

60. A use according to Claim 57 wherein said disease is gingivitis.

61. Use of a compound according to any one of Claims 1 to 30 in the manufacture of a medicament for use in treating a disease characterized by excessive cartilage or matrix degradation.

62. A use according to Claim 61 wherein said disease is osteoarthritis.

63. A use according to Claim 61 wherein said disease is rheumatoid arthritis.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07942

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :C07D 277/32; A61K 31/425
US CL :548/200; 514/365
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/200; 514/365

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | GOEL ET AL. Structure-activity study on antiinflammatory pyrazole carboxylic acid hydrazide analogs using molecular connectivity indices. J. Chem. Inf. Comput. Sci. 15 March 1995, Vol. 35, No. 3, pages 510-514, see Table 1, No. 30. | 1-3, 31, 52, 63 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| "E" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
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| "P" | document published prior to the international filing date but later than the priority date claimed | | |

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